Amendments to the Specification:

Please replace the paragraph at page 1, line 27 to page 2, line 14, with the following amended paragraph:

One general example of laboratory tools utlizes arrays of biopolymers, such as arrays of nucleic acids or proteins. For example, companies such as Affymetrix (e.g., VLSIPS® arrays; Santa Clara, CA), Hyseq (Mountain View, CA), Research Genetics (e.g., the GeneFilters® microarrays; Huntsville AL), Axon Instruments (GenePix®; Foster City, CA), Operon (e.g., OpArrays®, Alameda, CA) and others provide many technologies for making physical arrays of nucleic acids and other molecules. For example, arrays have been used for Disease Management issues, Expression Analysis, GeneChip Probe Array Technologies, Genotyping and Polymorphism analysis, Spotted Array Technologies and the like. ~~For a list of publications related to the topic of array construction and use, *see*, www.affymetrix.com/resources/scientific_paper.html~~ and ~~www.hyseq.com/company/ebibl.html.~~ Reviews of nucleic acid arrays include Sapolsky et al. (1999) "High-throughput polymorphism screening and genotyping with high-density oligonucleotide arrays." Genetic Analysis: Biomolecular Engineering 14:187-192; Lockhart (1998) "Mutant yeast on drugs" Nature Medicine 4:1235-1236; Fodor (1997) "Genes, Chips and the Human Genome." FASEB Journal 11:A879; Fodor (1997) "Massively Parallel Genomics." Science 277: 393-395; and Chee et al. (1996) "Accessing Genetic Information with High-Density DNA Arrays." Science 274:610-614.

Please replace the paragraph at page 2, lines 15-28 with the following amended paragraph:

Examples of protein-based arrays include immuno arrays (*see*, e.g., ~~http://arrayit.com/protein-arrays/;~~ Holt et al. (2000) "By-passing selection: direct screening for antibody–antigen interactions using protein arrays." Nucleic Acids Research 28(15) E72-e72), superproteins arrays ~~(*see*, e.g., www.jst.go.jp/erato/project/nts_P/nts_P.html)~~, yeast two and other "n" hybrid array systems (*see*, e.g. Uetz et al. (2000) "A comprehensive analysis of protein-protein interactions in Saccharomyces cerevisiae" Nature 403, 623-627, and Vidal and Legrain (1999) "Yeast forward and reverse 'n'-hybrid systems." Nucleic Acids Research 27(4) 919-929); the universal protein array or "UPA" system (Ge et al. (2000) "UPA, a universal protein array system

for quantitative detection of protein–protein, protein–DNA, protein–RNA and protein–ligand interactions." Nucleic Acids Research, 28(2): E3-e3) and the like. Commercial companies such as Ciphergen (Freemont, CA); ~~www.ciphergen.com,~~ Beckman Coulter Inc. (Brea, CA); and others also provide commercial protein chip arrays.

Please replace the paragraph at page 3, lines 3-9 with the following amended paragraph:

Many such automated systems are commercially available. For example, a variety of automated systems are available from the Zymark Corporation (Zymark Center, Hopkinton, MA), which utilize various Zymate systems ~~(*see also*, www.zymark.com/)~~, which typically include, e.g., robotics and fluid handling modules. Similarly, the common ORCA® robot, which is used in a variety of laboratory systems, e.g., for microtiter tray manipulation, is also commercially available, e.g., from Beckman Coulter, Inc. (Fullerton, CA).

Please replace the paragraph at page 21, line 27 to page 22, line 6 with the following amended paragraph:

The present invention also contemplates the use of naturally occurring and modified electron transport proteins to facilitate signal transduction. In nature, a variety of electrochemically active proteins are part of an electrochemical gradient in which the energy liberated, e.g., from light or food, is used to drive work until the electrons are delivered to the final electron sink, i.e., oxygen. The sole function of these proteins ~~(*see*, e.g., www.chem.qmw.ac.uk/iubmb/etp/)~~ is to take electrons at one redox potential and pass them on to another protein in a controlled way. An example of this is found in cytochrome P450 chemistry, which is described further in Example 5. In one example, the electrons originate in NADH where they reduce feredoxin reductase, which reduces feredoxin, which passes the electrons to the P450 itself. This cascade enables the biological system to control the electron transfer and prevent the electrons flowing at will (equivalent to shorting a battery).

Please replace the paragraph at page 74, lines 19-32 with the following amended paragraph:

In addition to those in Ausubel, examples of protein-based arrays include various advanced immuno arrays (*see*, e.g., ~~http://arrayit.com/protein-arrays/;~~ Holt et al. (2000) "By-passing selection: direct screening for antibody–antigen interactions using protein arrays~~.~~" Nucleic Acids

Research 28(15) E72-e72), superproteins arrays ~~(*see*, e.g., http://www.jst.go.jp/erato/project/nts_P/nts_P.html)~~, yeast two and other "n" hybrid array systems (*see*, e.g. Uetz et al. (2000) "A comprehensive analysis of protein-protein interactions in Saccharomyces cerevisiae" Nature 403, 623-627, and Vidal and Legrain (1999) "Yeast forward and reverse 'n'-hybrid systems." Nucleic Acids Research 27(4) 919-929); the universal protein array or "UPA" system (Ge et al. (2000) "UPA, a universal protein array system for quantitative detection of protein–protein, protein–DNA, protein–RNA and protein–ligand interactions." Nucleic Acids Research, 28(2): E3-e3) and the like. Commercial companies such as Ciphergen (Freemont, CA); ~~www.ciphergen.com~~, Beckman Coulter Inc. (Brea, CA); and others also provide commercial protein chip arrays.

Please replace the paragraph at page 83, lines 4-12 with the following amended paragraph:

Furthermore, companies such as Affymetrix (e.g., VLSIPS® arrays; Santa Clara, CA), Hyseq (Mountain View, CA), Research Genetics (e.g., the GeneFilters® microarrays; Huntsville AL), Axon Instruments (GenePix®; Foster City, CA), Operon (e.g., OpArrays®, Alameda, CA), Ciphergen (Freemont, CA); ~~www.ciphergen.com,~~ Beckman Coulter Inc. (Brea, CA), and many others provide diverse technologies for making physical arrays of nucleic acids, proteins and other molecules. For example, arrays have been used for Disease Management issues, Expression Analysis, GeneChip Probe Array Technologies, Genotyping and Polymorphism analysis, Spotted Array Technologies, and the like.

Please replace the paragraph at page 83, lines 13-32 with the following amended paragraph:

Several protocols for making arrays, e.g., of nucleic acids are also found on the internet, ~~e.g., at http://www.protocol-online.net/molbio/DNA/dna_microarray.htm,~~ in addition to the other references noted above. For example, this site provides relevant details regarding Protocols for Making Drosophila Arrays, PCR amplification of cDNAs for printing, polylysine slide preparation, "post-processing" and direct labeling of cdna probes, preparation of slides; preparation of dna samples, post-processing of arrays preparation of fluorescent DNA Probe from Yeast mRNA, preparation of fluorescent probe from human RNA preparation of fluorescent probe from *E. coli* RNA, preparation of fluorescent DNA probe from genomic DNA, cyanine dye HPLC purification,

modified eberwine ("antisense") RNA Amplification Protocol, hybridization of arrays, preparation of total RNA from cultured human cells preparation of PolyA+ mRNA from total Human RNA amplification and purification of cDNAs for microarray manufacture, microarray manufacture and processing, generating control mRNAs by In Vitro transcription; generating fluorescent cDNA controls by linear PCR, preparation of fluorescent probes from total human mRNA, cDNA microarray hybridization and washing, gene expression analysis with microarrays, mutation detection with oligonucleotide microarrays, comparative gene expression study using microarrays, microarray hybridization protocols, etc. Futher details regarding arraying methods are also found PCT/US01/01056, filed January 10, 2001.

Please replace the paragraph at page 92, line 11 to page 93, line 2 with the following amended paragraph:

The second basic method for acquiring nucleic acids does not rely on the physical pre-existance of a nucleic acid. Instead, nucleic acids are generated ~~synthetically~~ synthetically, e.g., using well-established nucleic acid synthesis methods. For example, nucleic acids can be synthesized using commercially available nucleic acid synthesis machines which utilize standard solid-phase methods. Typically, fragments of up to about 100 bases are individually synthesized, then joined (e.g., by enzymatic or chemical ligation methods, or polymerase mediated recombination methods) to form essentially any desired continuous sequence. For example, the polynucleotides and oligonucleotides of the invention can be prepared by chemical synthesis using, *e.g.*, the classical phosphoramidite method described by Beaucage *et al.*, (1981) Tetrahedron Letters 22:1859-69, or the method described by Matthes *et al.*, (1984) EMBO J. 3: 801-05., e.g., as is typically practiced in modern automated synthetic methods. According to the phosphoramidite method, oligonucleotides are synthesized, *e.g.*, in an automatic DNA synthesizer, assembled and, optionally, cloned in appropriate vectors. In addition, essentially any nucleic acid can be custom ordered from any of a variety of commercial sources, such as The Midland Certified Reagent Company (mcrc@oligos.com), The Great American Gene Company ~~(http://www.genco.com)~~, ExpressGen Inc. ~~(www.expressgen.com)~~, Operon Technologies Inc. (Alameda, CA) and many others. Similarly, peptides and antibodies (useful in various embodiments noted below) can be custom ordered from any of a variety of sources, such as PeptidoGenic (pkim@ccnet.com), HTI Bio-products, inc.

~~(http://www.htibio.com),~~ BMA Biomedicals Ltd (U.K.), Bio.Synthesis, Inc., Research Genetics (Huntsville, Alabama) and many others.

Please replace the paragraph at page 99, lines 17-22 with the following amended paragraph:

Various systems are also available for simultaneous synthesis and folding of complex proteins. For example, the control of redox potential, the use of helper proteins (from both bacterial and eukaryotic systems) and the like can be used to provide for improved cell free translation. In addition to the references noted above, additional details regarding cell free protein translation can be found ~~at http://chemeng.stanford.edu/html/swartz.htm~~.

Please replace the paragraph at page 100, line 31 to page 101, line 9 with the following amended paragraph:

In addition to array member identification, product identification or purification, and the like, such modules can also include an instruction set for discriminating between members of the array based upon detectable characteristics, such as a physical characteristic of the array members, bound test or control samples, array products, activities of members, bound components, products or reactants, and concentrations of the products or reactants. For example "hit picking" software is available which permits the user to select criteria to identify members of an array that display one or more activity which is sufficient to be of interest for further analysis, or to provide molecular signature information. For example, software for array analysis includes, e.g., Scanalyze® and NOMAD ~~(*see*, e.g., http://www.microarrays.org/software.html)~~, as well as many other packages.

Please replace the paragraph at page 103, lines 3-8 with the following amended paragraph:

Software for examining array patterns, determining reaction rates or monitoring formation of products by arrays are available or can easily be constructed by one of skill using a standard programming language such as Visualbasic, Fortran, Basic, Java, or the like, or can even be programmed into simple end-user applications such as Excel or Access. Software for array analysis is also commercially available, e.g., Scanalyze® and NOMAD ~~(*see*, http://www.microarrays.org/software.html)~~.

Please replace the paragraph at page 109, lines 13-20 with the following amended paragraph:

The Cytochrome P450 family is one of the largest and oldest superfamilies of enzymes known ~~(*see*, e.g., drnelson.utmem.edu/CytochromeP450.html)~~. It contains over 200 known families, thousands of sequences and several crystal structures. The superfamily is structurally and functionally well conserved but very diverse in sequence and substrate space ~~(*see*, e.g., drnelson.utmem.edu/PIR.P450.description.html)~~. Cytochrome P450 isozymes provide an example of a generic recognition element with a variety of substrate specificities, and a common mediator based electrochemical read out.

Please replace the paragraph at page 107, line 31 to page 108, line 4 with the following amended paragraph:

Alternative formats for performing detection assays, e.g., on microfluidic devices (e.g., LabMicrofluidic device® high throughput screening system (HTS) by Caliper Technologies, Mountain View, CA or the HP/Agilent technologies Bioanalyzer using LabChip™ technology by Caliper Technologies Corp. ~~*See*, also, www.calipertech.com)~~ are available and favorably employed in the context of the present invention.

Please replace the paragraph at page 110, lines 21-25 with the following amended paragraph:

In addition to the properties and features described above, the greatest single class of mediators of drug metabolism in humans are cytochrome P450s~~, *see*, e.g., www.georgetown.edu/departments/pharmacology/davetab.html~~. The specificities of these isozymes are well described and include most compounds of pharmaceutical importance.

Please replace the paragraph at page 111, lines 14-26 with the following amended paragraph:

Warfarin is a coumarin derivative with which no obvious flavin oxidase activity is associated in the literature. However, the interactions with cytochrome P450 have been well described. In vivo, Warfarin is oxidized by cytochrome P450 2C9, which is one of the major drug metabolizing isozymes described to date~~, *see*, e.g., www.georgetown.edu/departments/pharmacology/davetab.html~~. It is also oxidized by bacterial cytochrome P450 isozyme 105 D1. The latter enzyme has several closely related homologues in the

database many more should be accessible using well-known techniques. The domain structure of this protein has also been described ~~(www.expasy.ch/cgi-bin/get-sprot-entry P26911 , http://p450.abc.hu/P450domains.html)~~. P450 105D1 is derived from the bacterial species *S. griseus* and has a molecular weight of ~40 kDa. This isozyme has been expressed in *E. coli* at ~12 mg/L and has been shown to be active (if at reduced levels) after immobilization to DE 52 resin. (*see*, e.g., BBRC., 279, 708-711, 2000).

Please replace the paragraph at page 112, lines 3-11 with the following amended paragraph:

Purification and immobilization of the active proteins on an electrode array can be accomplished by any of the means described above, e.g., with respect to a glucose oxidase based sensor, with the exception that different redox mediator may be required or desirable. Alternative redox mediators are known in the art, and of skill in the art is able to empirically determine which candidate redox mediator is suitable for a particular application. It should be noted that the redox potential for P450 isozymes ~~(*see*, e.g., www.uky.edu/Pharmacy/ps/porter/CPR_enzymology.htm)~~ typically drops by ~100mV on substrate binding to ~-270mV and in most cases the electrons are provided to the P450 isozymes by reduced flavins.

Please replace the paragraph at page 112,lines 22-27 with the following amended paragraph:

The expected structure space covered by this initial library should overlap with the specificity of cytochrome 2C9. Further libraries that covered the structure space of the other important human P450s ~~(www.georgetown.edu/departments/pharmacology/davetab.html)~~ would then be constructed and finally an array of arrays would give the full spectrum of P450 specificities seen in man.